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10/525,955	03/31/2006	Bernd Rehm	3652-50	3076

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,955	REHM, BERND	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-98 and 100* is/are pending in the application.

4a) Of the above claim(s) *30-58,60-63,65-71,80,85,89,90,96-98 and 100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,64,72-79,81-84,86-88 and 91-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In response to a previous Office action (mailed on 1/11/2008), Applicants filed a response and amendment is received on April 28, 2008. Claims 59, 60, 81 are amended. Claims 30-98 and 100 are pending. Claims 1-29 and 99 remain canceled. Claims 30-58, 61-63, 65-71 and 96 remain withdrawn. A new claim, claim 100, is added. Claims 60 (PHA thiolase, etc), 80, 85, 89, 90, 97-98 and 100 (polymer particle forming proteins) comprise non-elected subject matters and therefore will not be examined and are withdrawn. Claims 59, 64, 72-79, 81-84, 86-88, 91-95 will be examined.

Applicants' arguments filed on April 28, 2008, have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections

35 U.S.C 112

35 U.S.C. 112 2nd paragraph

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 59, 64, 72-79, 81-84, 86-88, 91-95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 75 –"a lipid layer" "- is confusing as no such a lipid layer is defined in the particle produced by the method of claim 59.

Claims 59 and 99 the recitation "biologically active" makes the claim indefinite and vague. As it is unclear what "biologically active" term means. Applicants' argument for "biologically active" is considered but not found persuasive. Applicants argue that "biologically active protein is intended to encompass any protein that can "initiate a biological response on the part of the organism" including enzymes that "catalyse a specific reaction in the organism" and "proteins, such as for example antibodies" (see paragraph [0011]). The term "biologically active substance" is also intended to encompass any substance that may be bound by a binding domain or a coupling reagent. The above definition of the applicants for biologically active is unclear, what activity it refers to, activity of enzyme or an antibody are not same, similarly any substance that binds to a binding domain or coupling reagent may not comprise biological activity. Therefore "biologically active" is a vague term.

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35 U.S.C. 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59 64, 72-79, 81-84, 86-88, 91-95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 59, 64, 72-79, 81-84, 86-88, 91-95 are directed to a method of producing any polymer conjugates comprising polyhydroxy carboxylate conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell expressed with a fusion protein comprising any polymer synthase from any source or from Ralstonia, Alcaligenes or Pseudomonas, etc (claims 64, 74) and any biologically active substance or protein.

The specification fails to describe how to produce any polymer conjugates comprising any polyhydroxy carboxylate conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell expressed with a fusion protein comprising any polymer synthase and any biologically active substance or protein. The specification fails to describe in any fashion the physical (structural) and/or chemical properties of the claimed class of polymer particles, protein and biomolecules and their biological function. A biomolecule can be any molecule i.e., antibody, protein, enzyme, hormone, DNA, RNA, lectin, glycoprotein, bioactive small organic compounds, etc. Similarly, the specification fails to describe the structure of all polymer particles, biomolecules and protein. Conjugation of a polymer compound to a protein or biomolecule depends on the nature of functional

groups in those molecules that are to be conjugated. No relationship between the structure of all polymer compounds, and proteins is given in the specification. Moreover specification does not describe how any host cell can be used to make any polymer conjugates comprising any polymeric compound conjugated with any protein or any biologically active substance (any bioactive organic compound or protein). Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants argue that the claimed methods of production of polyhydroxy carboxylate particles having any surface bound protein or any biologically active substance using any host cell expressing a fusion protein comprising any polymer synthase and any biologically active protein is adequately described in the specification. They based their argument that specification discloses that a biologically active substance is a substance that has some sort of biological activity, such substance comprises Flag epitope, bioactive protein or enzyme, etc. They argue that host cell is described in the specification at (paragraph 0024, 0073) are Ralstonia eutropha, Escherichia coli, Pseudomonas, etc. However, this is not persuasive because the scope of biological active substance and host cell in the claim is much broader than what the specification describes. Moreover conjugation of a polymer compound to any protein or biomolecule depends on the nature of functional groups in those molecules that are to be conjugated, and no relationship between the structure of polymer compounds, and proteins is given in the specification.

Specification does not describe how any host cell can be used to made polymer conjugates comprising polyhydroxy carboxylate particles conjugated with any protein or any biologically active substance (any bioactive organic compound or protein). Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. Applicant also argue that structure of polymer synthase and biological active protein that used to make the fusion protein can be derived from the knowledge of prior art. This is not found persuasive. To make a fusion protein comprising polymer synthase and any other protein and expressing in a host cell require the structure of the respective proteins to be conjugated. Moreover such fusion protein comprising any polymer synthase conjugated to any bioactive protein comprise infinite number of combination as discussed above that specification does not describe As such the disclosed species are not representative of the structure and function of all members of the genus claimed.

Claims 59, 64, 72-79, 81-84, 86-88, 91-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a polymer conjugates comprising R-hydroxy butyric acid polymer compound conjugated with FLAG –PhaC1 fusion protein using E. coli expressed with plasmid pBBad-P containing *R. eutropha* polymer synthase and FLAG binding domain, does not reasonably provide enablement for method of producing any polymer conjugates comprising any polyhydroxy carboxylate compound conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell

expressed a fusion protein comprising any polymer synthase from any source or in the case of claims 64 and 74 from Ralstonia, Alcallgenes or Pseudomonas, etc and any biologically active substance or protein from any source. . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and for use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claim(s).

Claims 59, 64, 72-79, 81-84, 86-88, 91-95 are so broad as to encompass method of producing any polymer conjugates comprising any polyhydroxy carboxylate compound conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell expressed a fusion protein comprising any polymer synthase from any source or in the case of claims 64 and 74 from Ralstonia, Alcallgenes or Pseudomonas, etc and any biologically active substance or protein from any source . The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to any method of producing any polymer conjugates comprising any polymeric compound conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell expressed with any polymer synthase. In view of the great breaths of claims

59, 64, 72-79, 81-84, 86-88, 91-95, amount of experimentation required to make broad class of polymer conjugates comprising any polymeric compound conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell expressed with fusion protein comprising any polymer synthase and any biologically active substance, and the lack of guidance, working examples, unpredictability of the art in predicting the function (polymer synthase activity) from protein's structure (Whisstock, et al. Quarterly Rev. Biophy. 2003, 36, pp 307-340), the claimed invention would require undue experimentation. As such the specification fails to teach one of ordinary skill how to use the full scope of the claims.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method of few polymer conjugates, such as comprising R-hydroxy butyric acid polymer compound and FLAG epitope protein made by using *E. coli* expressed with plasmid pBBad-P containing *R. eutropha* polymer synthase and FLAG protein .

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the

desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass method of producing any polymer conjugates comprising any polymeric compound conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell expressed with any polymer synthase, because the specification does **not** establish: (A) regions of the protein structure which may be modified to make polymer particles (B) the general tolerance of modification and extent of such tolerance on polymer synthase activity; (C) a rational and predictable scheme for modifying any polymer synthase polypeptide amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including method of producing any polymer conjugates comprising any polymeric compound conjugated with any protein or any biologically active substance (any bioactive organic compound or protein) using any host cell expressed with any polymer synthase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of fusion proteins, having the

desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988).

Applicants contend that claims 59, 64, 72-79, 81-84, 86-88, 91-95 meet the enablement requirement of § 112, first paragraph. They argue that one of ordinary skill in the art would be able to carry out the invention as now claimed without the exercise of undue experimentation. In particular, the specification provides guidance on:(1) polymer synthase choice; (2) choice of biologically active substance or protein; (3) preparation of expression constructs; (4) transformation of host cells; and (5) culturing of host cells. It is not found persuasive because as discussed above the scope of biological active substance and host cell claimed in these claims is much broader than what the specification describes. Moreover conjugation of a polymer compound to any protein or biomolecule depends on the nature of functional groups in those molecules that are to be conjugated, and no relationship between the structure of polymer compounds, and proteins is given in the specification. Specification does not describe how any host cell can be used to made polymer conjugates comprising polyhydroxy carboxylate particles conjugated with any protein or any biologically active substance (any bioactive organic compound or protein). To make a fusion protein comprising polymer synthase and any other protein and expressing in a host cell require the structure of the respective conjugates. Applicant further argue that claimed methods is directed to the use of fusion protein comprising polymer synthase and other bioactive protein having ability to produce polyhydroxy carboxylate.

Applicants argue that specification describes, in example 6.2.1 and paragraph 0035-0036 fusion proteins, such as FLAG –PhaC1 fusion protein (example 6.2.1). A fusion of gene of FlAG epitope of SEQ ID NO. 10 with gene of polymer synthase of SEQ ID No. 11 (example 6.2.1) yields fusion gene of SEQ ID NO: 12. Plasmid pBHR71-FLAG (Fig. 13) containing the gene of SEQ ID No. 12 imparts expression of a polymer synthase with N-terminal FLAG fusion (this part of the protein now forms the binding domain). As example shows above, for making fusion protein the structures of both fusion partners are known (SEQ ID NO: 10 and 12). However claimed fusion protein in these claims has no structure. Therefore as discussed above the scope fusion protein comprising conjugation of any polymer synthase or polymer synthase of Ralstonia, Alcallgenes or Pseudomonas with any biologically active substance or protein claimed in these claims is much broader than what the specification describes. Moreover such fusion protein comprising any polymer synthase conjugated to any bioactive protein comprise infinite number of combination as discussed above that specification does not describe. As the structure of the claimed polymer synthase and bioactive protein that recite in the instant claims are not defined in any way, one of ordinary skill in the art would not be able to make and use any host cell comprising said fusion protein and require undue experimentation to find out which of these host cells produce polyhydroxy carboxylate particles having surface bound protein or biologically active substance.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of 59, 64, 72-75, under 35 U.S.C. 103(a) by Madison et al. (Microbiol Mol Biol rev 1999 vol.63, pp 21-53, from IDS) or Steinbuchel et al (US 6022729, from IDS) is maintained.

Madison et al. disclose processes for preparing polymeric particles from polyhydroxy alkanoates (PHAs) synthesized inter alia in Ralstonia eutropha and Escherichia coli (pages 37 and 42) using genes, such as polymer synthase, from the Ralstonia PHA biosynthetic pathway (pages 26-29), wherein fatty acids and other hydrocarbons (including those with functional side groups) may be used as substrates (pages 30-33). Further, they disclose that particle size is determined by the amount of particle-binding proteins present, including phasins (phaP) and PHA synthase, since phasin overexpression leads to an increased number of small particles, and that the molecular weight of the polymer is determined by the ratio of substrate to enzyme. However Madison et al. do not disclose the process for preparing polymeric particles having surface bound protein using organism expressing fusion protein comprising polymer synthase and other bioactive substance.

Steinbuchel et al disclose fusion protein comprising GA14-protein (a polymer synthase) and AcDH (acetaldehyde dehydrogenase) (page 16, lines 48-59) and transformed *E. coli* expressing said fusion protein. Steinbuchel et al also disclose that the acetaldehyde dehydrogenase binds to the surface of the polyhydroxy butyrate (PHB) granules in vivo in the transformed E. coli expressing said fusion protein.

As such it would have been obvious to one of ordinary skill in the art to use fusion protein comprising GA14-protein (polymer synthase) and AcDH and express in *E. coli* (as taught by Steinbuchel et al) and use the said *E. coli* for the method of production of PHA particles as taught by Madison et al. so that said produced PHA particles has surface bound protein (Steinbuchel et al)

Applicants argue that Madison does not teach fusion protein construct comprising polymer synthese and other bioactive protein. It is true that Madison does not teach fusion protein construct comprising polymer synthese and other bioactive protein but they teach method of production of polyhydroxyalkanoates (PHAs) using Ralstonia eutropha and Escherichia coli (pages 37 and 42) expressing polymer synthase. If it teach fusion protein comprising polymer synthese and other protein, it would be a USC 35 102 art. Applicants' argument that Steinbuchel et al (US 6022729) do not teach polymer synthese protein is not true. In fact they teach fusion protein comprising GA14-protein (polymer synthase) and aldehyde dehydrogenase.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public

PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah, PhD

Examiner, Art Unit 1652

Recombinant Enzymes, 3C31 Remsen Bld

400 Dulany Street, Alexandria, VA 22314

Telephone: 517-272-1261

/Rebecca E. Prouty/
Primary Examiner,
Art Unit 1652

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